IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

LAZAR et al.

Serial No. 10/672,280

Filed: September 26, 2003

For: *OPTIMIZED Fc VARIANTS AND METHODS FOR THEIR GENERATION*

Examiner: Chun Wu Dahle

Group No. 1644 Confirmation No.: 8317

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Victoria Poulsen

PRE-APPEAL BRIEF REQUEST FOR REVIEW

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Sir:

In accordance with 1296 Off. Gaz. Pat. Office 67 (July 12, 2005), Applicants request review of the Examiner's final rejections of: (a) claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142 and 144 under 35 U.S.C. § 103(a) over Presta (US Patent 6,737,056).

A species is patentable over a Genus

As stated in Takeda v. Alphapharm, 492 F.3d 1350, (Fed. Cir. 2007), the factors for evaluation of obviousness are:

> 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. KSR, 127 S.Ct. at 1734 (quoting Graham, 383 U.S. at 17-18, 86 S.Ct. 684).

The Court went on to say:

> The KSR Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the

> known options within his or her technical grasp." KSR, 127 S.Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." Id. That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try. (Emphasis added).

Applicants argue that this is very similar to the situation at hand. The Federal Circuit in *Takeda* started with a discussion of the differences between the prior art and the claims by discussing the selection of a compound as a lead compound. Following this line of reasoning, the first question is whether one of skill in the art would select S239A as a "lead compound" upon which to experiment in order to achieve better FcγR binding. Applicants submit that this is not likely, as S239A had decreased binding to four of the five tested receptors, with the fifth, FcRn, showing similar binding to wild-type[1].

The Federal Circuit went on to discuss the choice of the claimed compounds and stated:

> The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. page 1350

Again, Applicants argue the similarity of the present case. There is no motivation to make the specific amino acid modifications claimed in the present case, with or without functional language. As shown in *Takeda*, different changes had unpredictable outcomes. Here, the Presta reference itself shows that different amino acid substitutions at the same position render dramatically different results. For example, S267A shows increased binding to both FcγRII and FcγRIII, while S267G essentially eliminates FcγRIII binding. Another example is at position 269: E269A and E269Q both show decreased binding to FcγRIII, while E269D shows unchanged binding to FcγRIII. In addition, some amino acid modifications have no effect on binding at all, which is similarly unpredictable. For example, E318A (negatively charged amino acid replaced by small hydrophilic residue) and E318K (negatively charged amino acid replaced by positively charged amino acid residue) both show essentially no change in binding to any

[1] Applicants further note that the lack of a standard deviation number for the binding of S239A to FcRn also brings into question whether this variant actually does have similar binding to wild type.

FcγR. There are a number of additional examples within Presta to illustrate that this reference directly teaches the unpredictability of making amino acid changes.

Accordingly, even assuming, *arguendo*, that a prima facie case was made, the Applicants submit that these rebuttal arguments, in line with the Federal Circuit and Supreme Court positions on obviousness, render the claims patentable over Presta, whether the claims include functional language or not.

The teachings of the Presta reference as a whole

As stated in M.P.E.P. §2141.03 VI.,

> A prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention. (Emphasis in original).

There are 7 references in the specification that teach that amino acid modifications at position 239 will decrease binding to FcγRs:

> Of residues 233-239, P238 and S239 have been cited as possibly being involved in binding, but these two residues have never been evaluated by substitution or deletion. See column 3, lines 14-16.
>
> In one embodiment, the polypeptide variant with altered FcγR binding activity displays reduced binding to an Fc.gamma.R and comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. See column 5, lines 19.
>
> The polypeptide variant of interest may display reduced binding to an FcγRIII and comprise an amino acid modification at one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 293, 294, 295, 296, 301, 303, 322, 327, 329, 338, 340, 373, 376, 382, 388, 389, 416, 434, 435 or 437 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. (col 5, lines 23-30).
>
> Table 2 recites "reduced binding to both FcγRII and FcγRIII" includes 239.
>
> To generate an Fc region variant with reduced binding to the FcγR one may introduce an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382,

388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the Fc region. (See col 22, lines 55-61).

Fc region variants which display reduced binding to FcγRIII include those comprising an Fc region amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 293, 294, 295, 296, 301, 303, 322, 327, 329, 338, 340, 373, 376, 382, 388, 389, 416, 434, 435 or 437. (Column 23, lines 4-9).

Table 6 shows S239A has reduced binding to FcγRII (both FcγRIIA and FcγRIIB) and FcγRIIIA.

The sole reference to "increased binding" with a 239 variant is in claim 13, which **was not part of the application as filed.** The claims as filed have three claims that recite 239: original claim 14 is drawn to altered binding and recites a list of positions including 239; original claim 16 is drawn to reduced binding to an FcγR and recites a list of positions including 239; and original claim 18 is drawn to reduced binding to FcγRII and recites a list of positions including 239. Notably, original claim 23 is drawn to increased binding to an FcγR and does not recite position 239. Thus, the application as filed contains no disclosure of increased binding to any FcγR using a 239 variant.

The first time the concept of increased binding to an FcγR at position 239 was introduced was the amendment dated 12/3/02, when claim 14 changed the preamble from "altered binding" to "increased binding"; the proffered reason stated by the patentee is to conform to the restriction requirement. We note that the Applicants state that "the amendments do not introduce any new matter", a statement with which we clearly take issue.

The fact that this claim was not part of the original disclosure and is the **sole** disclosure relating to increased binding of a 239 variant lessens the strength of this teaching.

Taken together, the 7 references in the specification to **decreased** binding as a result of a change at position 239, weighed against a **single** reference that was not even part of the original disclosure, renders non-obvious claims directed to increased binding at position 239.

Applicants appreciate that "patents are relevant as prior art for all they contain" (see M.P.E.P. §2123). However, in this case, the fact that the sole teaching of increased binding using variants at position 239 was added through a preamble change during prosecution and was not contested does tip the analysis towards a finding that the reference, as a whole, does not render the claimed invention obvious.

Secondary Indicia of Non-Obviousness

As outlined by the Supreme Court in *KSR*, the secondary indicia of non-obviousness is still a relevant factor for consideration in determining non-obviousness. In this case, Applicants would like to point out the commercial success of this Fc technology, including variants at position 239.

Applicants have previously demonstrated that this technology has been licensed by a number of companies, including Genentech, Centocor, MedImmune, Boehringer Ingelheim, Roche, PDL, Chugai and Human Genome Sciences.

In fact, with specific reference to position 239, the Applicants respectfully point out that MedImmune is actually utilizing some of these variants, as evidenced by U.S. Publication No. 2008/0071063, claims 13-16, with specific 239 residues recited, including 239E, 239D, 239Q, 239N, 239F, 239T, 239H and 239Y (claim 14) and 239D (claim 16); Protein Design Labs as evidenced by WO 05102387A2, pages 50 – 51, with 239D, 239E, 239N, 239Q, 239F, 239T, 239H, and 239Y specifically recited at page 50, lines13-14; and Chugai as evidenced by U.S. Publication No. 2007/0087005, claims 3 -5, 9 and 10, with specific 239 residue aspartic acid (D) recited.

Conclusion

Prompt and favorable consideration of this Request is respectfully requested. If the Examiner believes, for any reasons, that personal communication will expedite prosecution of this application, Examiner and the Panel are invited to telephone the undersigned at the number provided below.

The Commissioner is authorized to charge any additional fees associated with this communication, including any necessary fees for extension of time or additional claims, and/or credit any overpayment to Deposit Account No. 50-0310 (Attorney Docket No. 067461-5121US).

Respectfully submitted,

Dated: 5/28/09

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